



General

Guideline Title

Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma.

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Dec. 45 p. (Technology appraisal guidance; no. 268).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Advanced (unresectable or metastatic) melanoma

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Dermatology

Family Practice

Internal Medicine

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of ipilimumab for previously treated advanced (unresectable or metastatic) melanoma

Target Population

Adults with advanced, unresectable stage III or stage IV malignant melanoma who had been previously treated

Interventions and Practices Considered

Ipilimumab

Major Outcomes Considered

- Clinical effectiveness
 - Overall survival
 - 1-year survival
 - Progression-free survival
 - Best overall response rate
 - Modified World Health Organisation (WHO) criteria
 - Duration of response
 - Adverse events
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Manufacturer's Search Strategy

The manufacturer's submission (MS) reports the conduct of two systematic reviews of the literature to identify relevant clinical evidence related to ipilimumab. The first was conducted early in the development of the submission and spanned 1970 to April 8, 2010 and the second is a review update to cover the period of January 2010 to May 2011. Three electronic databases were searched (Medline, EMBASE and the Cochrane Library). Search terms appropriately included a combination of free-text and index terms combined with drug name used as free-text. The search strategies were reviewed and considered to be appropriate.

In addition, three sets of conference abstracts (first review) including American Society of Clinical Oncology (ASCO, annual meetings 2008-2010), European Society of Clinical Oncology (ESMO, annual meetings 2008-2010) and European Association of Dermato-Oncology (EADO, annual meetings 2008-2010) were searched. Additional conference sites that were also searched included: Perspectives in Melanoma (2008-2011) and Annual International Congress of the Society for Melanoma Research (2008-2011).

Given that it is likely that for all clinical studies in this area the manufacturer will have sponsored the trial or at least supplied the drugs, it is somewhat surprising that the manufacturer did not include a search of their own internal database of studies.

Critique of Manufacturer's Inclusion Criteria and Study Selection

The inclusion criteria for the review of the evidence were provided by the manufacturer and were appropriate. However, there were inconsistencies in the reporting of the decisions taken during the application of the review inclusion criteria. Although the review inclusion criteria indicated that trials with comparator treatments would be included in fact only trials that provided evidence related to ipilimumab were ultimately considered.

The MS concludes that two trials should be included for consideration of clinical effectiveness; MDX010-20 referred to as Hodi 2010 and CA184-022 referred to as Wolchok 2010. The first is a randomised double blind phase III trial while the second is a phase II dose ranging trial. It is worth noting that there is an internal inconsistency in the document whereby the inclusion of this second trial is listed as presenting either clinical or only safety data.

The inclusion criteria for the literature search were limited to randomised controlled trials (RCTs) of second-line treatments (explicitly excluding studies with mixed first and second-line treatment). However, the MS indicates that study CA184-007 which is referred to as Weber 2009 was selected to provide safety and tolerability data. This trial includes a mixed population of treatment naive and previously treated patients and used a dose of ipilimumab that is three times larger than the dose being considered in this appraisal; the trial also included use of a steroid in one arm to test whether the steroid decreased the number of adverse events (AEs) experienced by patients. No other rationale for the use of this trial is provided.

The ERG identified at least one other RCT that included a mixed treatment population where patients in one arm of the trial received the dose of ipilimumab being considered in this appraisal. The results of this study were found on-line through the manufacturer's website but no publication of the results was identified. In addition there is a single arm trial of patients receiving second-line treatment with a 10 mg/kg dose of the drug that might have provided comparative safety data.

A recent independent review identified the same published studies as the searches run by the manufacturer and the ERG. The ERG is therefore confident that no other relevant published studies were missed in the search. As noted above the ERG identified one unpublished study that is not mentioned in the submission, the results of which could have expanded the data available for analysis but it is unlikely that its inclusion would have changed the outcomes.

Economic Evaluation

Overview of Manufacturer's Cost-Effectiveness Review

The MS provides a brief description of the review of published cost-effectiveness evidence undertaken by the manufacturer. The databases searched and the search terms used appear to be reasonable and both inclusion and exclusion criteria are explicitly stated. The search by the manufacturer did not identify any relevant studies for inclusion in the review. Although there is no mention of searching within in-house databases for relevant studies, the ERG is confident that no relevant published studies are available for inclusion in the review.

Number of Source Documents

Clinical Effectiveness

Three randomized controlled trials were included.

Cost-Effectiveness

A manufacturer's model was submitted.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Included Studies

The manufacturer's submission (MS) provided a quality assessment of the included trials and these are presented in Appendix 1 of the ERG report (see the "Availability of Companion Documents" field).

Critique of Submitted Evidence Syntheses

This is a relatively new drug which has been investigated in manufacturer sponsored studies. The MS provides the results of a search for studies that is appropriate except for the fact that a search of their own internal databases was not reported. Given that the manufacturer holds the data related to the studies conducted to assess the effectiveness of ipilimumab it might have made more extensive use of its own database to identify unpublished studies or to identify data related to drug safety. The rationale for the selection of study CA184-07 to provide safety data is not immediately apparent.

Data are descriptively presented with no attempt to combine the data, which is appropriate given the heterogeneity between studies (e.g., differences in drug doses and comparators). The MS is limited by the fact that no studies were identified that included ipilimumab compared to any of the comparators listed in the final scope issued by NICE although the MS makes a case that the gp100 vaccine is clinically equivalent to best supportive care (BSC). Data from the pivotal study demonstrated an overall survival (OS) benefit in favour of ipilimumab+gp100 over

gp100+placebo and ipilimumab+placebo over gp100+placebo.

See Section 4 of the ERG report for more information on clinical effectiveness evaluation.

Economic Evaluation

Description of Manufacturer's Economic Model

The manufacturer constructed an EXCEL-based cost-utility model. The model is a cohort model with one cohort receiving ipilimumab and the other cohort receiving BSC. The approach used in the evaluation is a "partitioned-survival" model and is similar to a Markov cohort model. However, unlike a Markov model in which the transitions are modelled explicitly using transition probabilities, the "partitioned-survival" model calculates the proportion of patients in each treatment cohort that are expected to be in each health state at any time after treatment initiation.

There are four mutually exclusive states in the model: baseline disease, non-progressive disease, progressive disease, and death. Figure 4 of the ERG report (see the "Availability of Companion Documents" field) shows the model health states.

Model Validation

The manufacturer details a number of steps that were taken to validate the model including:

- Estimates of progression-free survival (PFS) and OS from the final model were checked against values calculated in a separate spreadsheet – results were the same
- Extensive one-way sensitivity analyses were conducted on all model inputs and results were reviewed to ensure that changes in cost and effectiveness measures were consistent with expectations, given model specifications
- Random checks were made on model inputs compared with source data
- In terms of internal validity, as noted above the survival functions used to generate estimates of PFS and OS for ipilimumab are very close to those obtained based on the empirical (Kaplan-Meier) survival distributions.

In addition, the model was presented (face-to-face) to four practicing UK clinicians to check the face validity of the model. The model was also presented to an advisory board of six UK health economists. Finally, the model was checked by a senior health economist. The manufacturer considered the feedback from all of those involved in the peer-review process and changes were made to the model and documentation where appropriate.

Sensitivity Analyses

The manufacturer carried out a wide range of sensitivity analysis: one-way sensitivity analysis, scenario analysis, and probabilistic sensitivity analysis (PSA).

One-way sensitivity analysis: the manufacturer conducted deterministic analysis on key variables (n=16) using the 5% and 95% confidence intervals for the variables considered. The only variable not included in the sensitivity analysis was the dose (mg/kg) of ipilimumab as this dose is fixed.

Scenario analysis: eight different scenario analyses are discussed in the MS and are described in the MS.

Probabilistic sensitivity analysis was conducted by repeated sampling; 1000 Monte-Carlo simulations were performed to provide sufficient runs to allow PSA results to stabilise.

See Section 5 of the ERG report (see the "Availability of Companion Documents" field) for details on manufacturer's economic evaluation and its critique by ERG.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The manufacturer developed a model in which people treated with ipilimumab were compared with those who received best supportive care.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee noted that the manufacturer assumed that the gp100 vaccine was clinically comparable to best supportive care and used the efficacy estimates from the gp100 arm in the MDX010-20 trial to inform model inputs. The Committee agreed with the clinical specialists that gp100 was likely to be an acceptable proxy for best supportive care in the model.

The length of follow-up in the MDX010-20 trial was too short to provide robust evidence of the overall survival gain beyond the length of the trial. The Committee expressed confidence in the data from the MDX010-20 trial, supported by data from 3 smaller trials, but noted that beyond this time period the calculation of overall survival gain was dependent on the modelling approach used for extrapolation.

The Committee accepted that the supplementary advice for appraising a life-extending end-of-life treatment applies, and that the manufacturer's incremental cost-effectiveness ratio (ICER) of £42,200 per quality-adjusted life-year (QALY) gained was plausible, but recognised that it could be higher using other approaches to modelling overall survival. On balance, the Committee considered that, given the robust clinical data available for a period of 50 to 70 months, the likelihood of long-term effectiveness in a small proportion of patients and the innovative nature of ipilimumab,

it could be concluded that ipilimumab is a cost-effective use of National Health Service (NHS) resources.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values

EORTC-QLQ and SF-36 data were collected in the MDX010-20 trial. The Committee noted the evidence review group's concerns that the number of respondents to the questionnaires dropped off considerably after week 12 in the MDX010-20 trial and that there was little difference between the utilities assigned to the progression-free and the progressive disease health states. The Committee noted that additional sensitivity analyses conducted by the manufacturer in response to the appraisal consultation document showed that the utility assumed for the progressive disease state was not a major driver of cost effectiveness. The Committee concluded that the utility estimates derived by the manufacturer were acceptable.

Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

No specific groups were identified for whom ipilimumab was particularly cost effective.

What Are the Key Drivers of Cost Effectiveness?

The Committee noted that the approach to modelling overall survival was the key driver of cost effectiveness for ipilimumab.

Most Likely Cost-Effectiveness Estimate (Given as an ICER)

The Committee concluded that the manufacturer's ICER of £42,200 per QALY gained was a plausible estimate, but recognised that the ICER could be higher using other approaches to overall survival modelling.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this submission by the Evidence Review Group. For clinical effectiveness, three randomised controlled trials were the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma

Potential Harms

Ipilimumab is most commonly associated with adverse reactions resulting from increased or excessive immune activity including diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain.

For full details of side effects and contraindications, see the summary of product characteristics available at <http://emc.medicines.org.uk/>

Contraindications

Contraindications

For full details of side effects and contraindications, see the summary of product characteristics available at <http://emc.medicines.org.uk/>

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- The technology in this appraisal may not be the only treatment for advanced (unresectable or metastatic) melanoma recommended in NICE guidance, or otherwise available in the NHS. Therefore, if a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set

out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with the paragraph above) when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.

- NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on the NICE Web site (<http://guidance.nice.org.uk/TA268>).
- A costing statement explaining the resource impact of this guidance.
- The Department of Health and the manufacturer have agreed that ipilimumab will be offered to the NHS under a patient access scheme that makes ipilimumab available with a discount on the list price. The size of the discount is commercial-in-confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Bristol Myer-Squibb (01244 586250, mg-ukpasadmin@bms.com).

Implementation Tools

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Dec. 45 p. (Technology appraisal guidance; no. 268).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\)](#) Web site .

Availability of Companion Documents

The following is available:

- Ipilimumab for previously treated unresectable malignant melanoma. Evidence Review Group report. Liverpool (UK): Liverpool Reviews and Implementation Group, University of Liverpool; 2011 Feb 19. 83 p. Electronic copies: Available from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#) .
- Ipilimumab for previously treated unresectable malignant melanoma. Costing statement. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Dec 12. 4 p. (Technology appraisal 268). Electronic copies: Available from the [NICE Web site](#) .

Patient Resources

The following is available:

- Ipilimumab for previously treated advanced melanoma. Information for the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Dec. 6 p. (Technology appraisal 268). Electronic copies: Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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